

CLINICAL STUDY PROTOCOL

A PHASE 1 OPEN-LABEL, TWO-ARM, DRUG-DRUG INTERACTION STUDY TO EVALUATE THE EFFECT OF ITRACONAZOLE AND RIFAMPIN ON THE PHARMACOKINETICS OF TALAZOPARIB IN PATIENTS WITH ADVANCED SOLID TUMORS

[REDACTED]

Sponsor Code: MDV3800-04
CCI Code: MVE011PC-160116
EudraCT Number: 2016-001813-26
IND Number: 108708

Investigational Product	Talazoparib (also known as MDV3800, BMN 673)
Clinical Phase	1
Indication to be studied	Solid tumors

SPONSOR	Medivation, Inc. and its Subsidiaries 525 Market Street, 36th Floor San Francisco, CA 94105 USA
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CONTRACT RESEARCH
ORGANIZATION

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[REDACTED]
Germany

CLINICAL SITES	Hungary (1 site) Poland (up to 3 sites) Russia (up to 3 sites) Moldova (1 site)
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Version Final 3.0, 11-Oct-2016

This study will be performed in compliance with the principles of Good Clinical Practice.

PROTOCOL SIGNATURE PAGE – Sponsor

This Clinical Study Protocol has been reviewed and approved by the Sponsor representatives listed below. Any modification of the Clinical Study Protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

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PPD [redacted] Regulatory Affairs

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Date:

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PROTOCOL SIGNATURE PAGE – Principal Investigator

I have read this protocol, and I agree that it contains all necessary details for me and my staff to conduct this study as described.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as an Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Principal Investigator

Name

Surname, (academic degree)

PPD

Signature:

PPD

Date:

PPD

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In case of a serious adverse event (See [Appendix 8.2.3](#)), the Principal Investigator will send a “Serious Adverse Event Report Form” and forward, within 24 hours of notification awareness, to Medivation Medical Monitor and to Medivation’s PPD [REDACTED] AND to the Medivation Medical Monitor for this study. as noted below :

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SYNOPSIS

Study Title

A PHASE 1 OPEN-LABEL, TWO-ARM, DRUG-DRUG INTERACTION STUDY TO EVALUATE THE EFFECT OF ITRACONAZOLE AND RIFAMPIN ON THE PHARMACOKINETICS OF TALAZOPARIB IN PATIENTS WITH ADVANCED SOLID TUMORS

Short Study Title

Talazoparib Drug-Drug Interaction Study

Study Codes

Sponsor Code: MDV3800-04
CCI Code: MVE011PC-160116
EudraCT Number: 2016-001813-26
IND Number: 108708

Sponsor

Medivation, Inc. and its Subsidiaries
525 Market Street, 36th Floor
San Francisco, CA 94105
USA

Contract Research Organization

CCI [REDACTED]
[REDACTED]
[REDACTED] Germany

Clinical Sites

Hungary (1 site)
Poland (up to 3 sites)
Russia (up to 3 sites)
Moldova (1 site)

Objectives**Primary:**

- To separately assess the effect of P-glycoprotein (P-gp) inhibitor (itraconazole) and P-gp inducer (rifampin) on the single-dose pharmacokinetics (PK) of talazoparib in patients with advanced solid tumors.

Secondary:

- To assess the safety and tolerability of a single dose of talazoparib with and without itraconazole or rifampin in patients with advanced solid tumors.

Design and Treatments

This is a Phase 1, open-label, two-armed, fixed-sequence drug-drug interaction (DDI) study in patients with advanced solid tumors for the investigation of the effect of P-gp inhibition and induction on the PK of talazoparib. Talazoparib is a substrate for P-gp, and itraconazole as well as rifampin will be used as a potent inhibitor and a potent inducer of P-gp, respectively. This study will evaluate the effect of multiple doses of itraconazole or rifampin on the pharmacokinetic profile of a single dose of talazoparib in patients with advanced solid tumors. A secondary objective is to evaluate the safety and tolerability of these combinations. All study subjects will be monitored for adverse events (AE) throughout the study.

The study will enroll approximately 18 subjects per arm (total of 36 subjects).

- Arm A: Subjects will receive a single oral dose of 0.5 mg talazoparib on Day 1 of Period 1, followed by a 14-day wash-out (Days 2–15). An oral dose of 100 mg itraconazole will be administered twice daily for 7 days (Days 16–22). In Period 2, on Day 23, a single dose of 0.5 mg talazoparib will be co-administered with 100 mg itraconazole in the morning, followed by 100 mg itraconazole alone in the evening. Oral doses of 100 mg itraconazole twice daily will continue throughout Days 24–36. For both periods, subjects will receive talazoparib under fasted conditions, defined as an overnight fast of at least 8 hours. No food will be allowed for at least 2 hours post-dose. Water is allowed as desired.
- Arm B: Subjects will receive a single oral dose of 1 mg talazoparib on Day 1 of Period 1, followed by a 14-day wash-out (Days 2–15). Oral doses of 600 mg rifampin will be administered once daily for 9 days (Days 16–24). In Period 2, on Day 25, a single oral dose of 1 mg talazoparib will be co-administered with 600 mg rifampin. Rifampin 600 mg once daily will continue throughout Days 26–38. For both periods, subjects will receive talazoparib under fasted conditions as defined above.

Subjects participating in this study with no clinically significant toxicities may be eligible to continue treatment on a separate extension protocol (MDV3800-13). Safety data for all subjects who had received any amount of talazoparib will be analyzed in the safety analyses for this study.

Study Assessments

Serial blood samples will be collected for PK analysis at pre-determined times after talazoparib administration, up to 336 hours (14 days). Blood samples for PK analysis will be drawn at the following selected time-points during each treatment period: pre-dose and 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264, and 336 hours after talazoparib dosing in both arms.

Key Eligibility Criteria

This study will enroll patients with advanced solid tumors who are at least 18 years of age and provide informed consent. Subjects must abstain from the use of any drugs with potential P glycoprotein (P-gp) interaction within 7 days or 5 half-lives (whichever is longer) before Day 1. Subjects must not have eGFR (estimated glomerular filtration rate) ≤ 50 mL/min/1.73 m² by the MDRD equation (Modification of Diet in Renal Disease [available via www.mdrd.com]) at screening and baseline, human immunodeficiency virus (HIV), hepatitis B, or hepatitis C. Subjects who had major surgery within 8 weeks before screening, or received any investigational or anti-cancer drug within 28 days before screening are excluded. Female and male subjects of childbearing potential must agree to use a highly effective birth control method starting 21

days before the first dose of study drug through 45 and 105 days after last dose of study drug, respectively.

Duration of Study

Approximately 13 weeks for each subject: 4 weeks screening period, approximately 5 weeks of treatment, and follow-up approximately 4 weeks after last talazoparib dose.

Sample Size Considerations

Based on the population PK analysis, the intra-subject variability is estimated to be 42% in terms of percent coefficient of variation (%CV). With a sample size of 15 evaluable subjects, the precision or half width of the 90% confidence interval (CI) for Test-Reference comparison on a log scale will be 0.259 from the observed difference in means. This calculation is based on an analysis of variance (ANOVA) model including effects of treatment and subjects nested within the sequence. When the true ratio is 1, the equivalence limits are 0.77 and 1.30. Eighteen subjects will be enrolled in each treatment group to allow for 15% of early discontinuation or loss to follow up. Subjects who discontinue prior to completion of both periods may be replaced upon agreement of the Investigator and the Sponsor.

Test Product

Talazoparib CCI

Talazoparib will be administered orally as a single-dose alone at 0.5 mg and in combination at 0.5 mg with itraconazole in Arm A, and as a single-dose alone at 1 mg and in combination at 1 mg with rifampin in Arm B.

Interactors

Itraconazole (P-gp Inhibitor)

Dosage form: capsule for oral administration
Strength: 100 mg
Dose: 100 mg itraconazole, twice daily, for 21 days

Rifampin (P-gp Inducer)

Dosage form: film coated tablet for oral administration
Strength: 600 mg
Dose: 600 mg rifampin, once daily, for 23 days

Statistical Methods

Pharmacokinetic Analyses

PK parameters (AUC_{0-inf} , AUC_{0-last} , C_{max} , T_{max} , $T_{1/2}$, k_{el} , CL/F , and V_d/F) will be calculated of talazoparib plasma concentrations using a non-compartmental analysis. Statistical analyses will be performed to assess the effect of steady-state itraconazole and rifampin on the pharmacokinetics of talazoparib using the treatment in combination with talazoparib as Test and the treatment with talazoparib alone as Reference. Only subjects with data for both Reference and Test treatments will be included in the analysis. A linear mixed effects model that includes treatment as a fixed factor and subjects nested within the sequence as a random factor will be fitted to the log transformed PK parameters (AUC_{0-inf} , AUC_{0-last} and C_{max}). A point estimate and the corresponding 90% CI for the difference between least squares means of Test and Reference treatment (Test – Reference) will be calculated. The antilogarithm of this value will be calculated to obtain the point estimate and the 90% CI for the ratio (Test/Reference) of the geometric means on the untransformed scale.

Efficacy Analyses

No efficacy analyses are planned in this study, although baseline tumor assessments will be obtained in the event that subjects choose to continue talazoparib treatment on a separate open label extension protocol.

Safety Analyses

All safety analyses will be performed using the safety population, defined as all subjects who received at least one dose of talazoparib. Safety will be evaluated using summaries of AEs, physical examinations (and weight), vital signs, electrocardiograms (ECGs), and laboratory evaluations.

AEs will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the National Cancer Institute Common Terminology Criteria for AEs (CTCAE Version 4). The number and percentage of subjects with AEs will be presented by MedDRA system organ class and preferred term, relationship to study treatment, severity, seriousness, and outcome (e.g., leading to permanent treatment discontinuation).

Adverse events will be recorded following the first dose of study drug (Day 1) until completion of the follow up visit. Serious adverse events will be collected starting at Informed Consent Signing until completion of the follow-up visit.

Laboratory values will be classified by severity using the CTCAE. Laboratory shift tables of baseline results to each subsequent visit will be produced as appropriate. Change from baseline in laboratory values will be tabulated and summarized graphically.

Table 1 Schedule of Assessments Arm A (Itraconazole Arm)

Study Day►	Screening	Baseline	Period 1														
	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Event▼																	
Ambulatory	X					X	X	X		X		X		X			X
Confinement		X	X	X	X												
Informed consent, SCR Number ¹	X																
ECOG assessment	X	X															
Tumor assessments	X																
Medical history	X	X															
Demographics	X																
Eligibility criteria / confirmation	X	X															
Enrollment		X															
Physical examination	X	X								X ²							X ²
Height	X																
Weight	X		X ³														X
12-Lead ECG	X	X	X ⁴														X
Vital signs ⁵	X	X	X ⁴	X	X					X							X
Adverse event review ⁶			X ³	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X ³	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer talazoparib			X														
Alcohol breath test	X	X															
Urine drug screen	X	X															
Serology for HIV, hepatitis B and C	X																
Serum pregnancy test ⁷	X	X															
Follicle-stimulating hormone ⁸	X																
Serum chemistry	X	X		X													X
Hematology	X	X		X													X

Table 1 Schedule of Assessments Arm A (Itraconazole Arm)

	Screening	Baseline	Period 1														
Study Day►	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Event▼																	
Coagulation	X																
Urinalysis	X	X		X													X
eGFR Calculation ⁹	X	X															
Blood sample for PK ¹⁰			X	X	X	X	X	X		X		X		X			X

1 Informed consent can be obtained on a separate visit

2 Symptom-oriented physical examination

3 On Day 1 pre-dose

4 On Day 1, pre-dose and 2 hours post-dose. Pre-dose ECG is triplicate 1 – 2 minutes apart (all other ECG recordings are single)

5 Vital signs comprise supine blood pressure, heart rate, body temperature, respiratory rate after ≥5 minutes rest

6 SAE will be collected starting from informed consent signature of the subject; non-serious AEs will be collected following the first dose of study drug on Day 1.

7 Collect only for females of childbearing potential.

8 Collect only for females with no spontaneous menses for ≥12 months, who are <55 years old, and who do not have documented surgical sterilization.

9 Calculation of the estimated glomerular filtration rate (eGFR) by MDRD equation.

10 For details see [Table 3](#)

SCR: screening; HIV: human immunodeficiency virus; PK: pharmacokinetics

Table 1 Schedule of Assessments Arm A (Itraconazole Arm) continued

	Period 2																	F/u ¹
Study Day▶	16-21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	
Event ▼																		
Ambulatory						X	X	X		X		X		X			X	X
Confinement		X	X	X	X													
Confirmation of eligibility		X																
Physical examination		X ²								X ²							X	
Weight			X ³														X	
12-Lead ECG		X ⁴	X ⁴	X						X							X	
Vital signs ⁵		X ³	X ³	X ³	X ³					X ³							X	X
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer talazoparib			X															
Administer itraconazole	X	X	X ⁶	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry		X		X						X							X	X
Hematology		X		X													X	X
Urinalysis		X		X													X	X
Blood sample for PK ⁷			X	X	X	X	X	X		X		X		X			X	

1 Follow-up visit 20±3 days after the last dose of itraconazole. In the event of early withdrawal of a subject, the follow-up contact should occur no sooner than 30 days after the last dose of talazoparib, unless the subject enrolls directly in the extension study, in which case the follow-up may occur earlier. If the subject is eligible to and chooses to participate in the separate open-label extension study and the screening for the open label extension study occurs within 30 days after the last dose of talazoparib, the follow up visit will not be required.

2 Symptom-oriented physical examination

3 Pre-dose

4 Triplicate ECG (1 to 2 minutes apart); before and 2.5 hours after itraconazole dose on Days 22 and 23 (all other ECG recordings are single in the morning at pre-dose, if applicable)

5 Vital signs comprise supine blood pressure, heart rate, body temperature, respiratory rate after ≥5 minutes rest

6 Itraconazole to be administered 30 minutes before talazoparib

7 For details see [Table 3](#)

F/u: follow-up; PK: pharmacokinetics

Table 2 Schedule of Assessments Arm B (Rifampin Arm)

Study Day►	Screening	Baseline	Period 1														
	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Event▼																	
Ambulatory	X					X	X	X		X		X		X			X
Confinement		X	X	X	X												
Informed consent, SCR Number ¹	X																
ECOG assessment	X	X															
Tumor assessments	X																
Medical history	X	X															
Demographics	X																
Eligibility criteria / confirmation	X	X															
Enrollment		X															
Physical examination	X	X								X ²							X ²
Height	X																
Weight	X		X ³														X
12-Lead electrocardiogram	X	X	X ⁴														X
Vital signs ⁵	X	X	X ⁴	X	X					X							X
Adverse event review ⁶			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer talazoparib			X														
Alcohol breath test	X	X															
Urine drug screen	X	X															
Serology for HIV, hepatitis B and C	X																
Serum pregnancy test ⁷	X	X															
Follicle-stimulating hormone ⁸	X																
Serum chemistry	X	X		X													X
Hematology	X	X		X													X

Table 2 Schedule of Assessments Arm B (Rifampin Arm)

	Screening	Baseline	Period 1														
Study Day►	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Event▼																	
Coagulation	X																
Urinalysis	X	X		X													X
eGFR Calculation ⁹	X	X															
Blood sample for PK ¹⁰			X	X	X	X	X	X		X		X		X			X

- 1 Informed consent can be obtained on a separate visit
- 2 Symptom-oriented physical examination
- 3 On Day 1 pre-dose
- 4 On Day 1, pre-dose and 2 hours post-dose. Pre-dose ECG is triplicate 1 – 2 minutes apart (all other ECG recordings are single)
- 5 Vital signs comprise supine blood pressure, heart rate, body temperature, respiratory rate after ≥5 minutes rest
- 6 SAE will be collected starting from informed consent signature of the subject; non-serious AEs will be collected following the first dose of study drug on Day 1.
- 7 Collect only for females of childbearing potential.
- 8 Collect only for females with no spontaneous menses for ≥12 months, who are <55 years old, and who do not have documented surgical sterilization.
- 9 Calculation of the estimated glomerular filtration rate (eGFR) by MDRD equation
- 10 For details see [Table 3](#)

SCR: screening; HIV: human immunodeficiency virus; PK: pharmacokinetics

Table 2 Schedule of Assessments Arm B (Rifampin Arm) continued

	Period 2																	F/u ¹
Study Day▶	16–23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	
Event▼																		
Ambulatory						X	X	X		X		X		X			X	X
Confinement		X	X	X	X													
Confirmation of eligibility		X																
Physical examination		X ²								X ²							X	
Weight			X ³														X	
12-Lead electrocardiogram		X ⁴	X ⁴	X						X							X	
Vital signs ⁵		X ³	X ³	X ³	X ³					X ³							X	X
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer talazoparib			X															
Administer rifampin	X	X	X ⁶	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry		X		X													X	X
Hematology		X		X													X	X
Urinalysis		X		X													X	X
Blood sample for PK ⁷			X	X	X	X	X	X		X		X		X			X	

1 Follow-up visit 20±3 days after the last dose of rifampin. In the event of early withdrawal of a subject, the follow-up contact should occur no sooner than 30 days after the last dose of talazoparib, unless the subject enrolls directly in the extension study, in which case the follow-up may occur earlier. If the subject is eligible to and chooses to participate in the separate open-label extension study, and the screening for the open label extension study occurs within 30 days after the last dose of talazoparib, the follow up visit will not be required

2 Symptom-oriented physical examination

3 Pre-dose

4 Triplicate ECG (1 to 2 minutes apart); before and 2.5 hours after rifampin dose on Days 24 and 25 (all other ECG recordings are single in the morning at pre-dose, if applicable).

5 Vital signs comprise supine blood pressure, heart rate, body temperature, respiratory rate after ≥5 minutes rest

6 Rifampin be administered 30 minutes before talazoparib

7 For details see [Table 3](#)

F/u, follow-up; PK, pharmacokinetic.

Table 3 Talazoparib Pharmacokinetic Sampling Schedule

Sample collection time relative to talazoparib dosing				
Study Day				Time point
Period 1		Period 2		
Arm A	Arm B	Arm A	Arm B	
1	23	25		pre-dose
				+0.50 h
				+1 h
				+2 h
				+4 h
				+8 h
				+12 h
2		24	26	+24 h
3		25	27	+48 h
4		26	28	+72 h
5		27	29	+96 h
6		28	30	+120 h
7		29	31	
8		30	32	+168 h
9		31	33	
10		32	34	+216 h
11		33	35	
12		34	36	+264 h
13		35	37	
14		36	38	
15		37	39	+336 h

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
ADP	Adenosine diphosphate
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
anti-HBc[+]	anti-hepatitis B core antigen [positive test result]
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BER	Base excision repair
BRCA	Breast cancer susceptibility gene
CI	Confidence interval
CL _{CR}	Creatinine clearance
CPK	Creatine phosphokinase
CPMP	Committee for Proprietary Medicinal Products; current name: Committee for Medicinal Products for Human Use (CHMP)
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Co-Operative Oncology Group [Performance Status]
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HBsAg[+]	Hepatitis B surface antigen [positive test result]
HCV[+]	Hepatitis C virus [positive test result]
HIV[+]	Human immunodeficiency virus [positive test result]
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MGMT	Methylguanine methyltransferase
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association
PARP	Poly(ADP ribose) polymerase
PDF	Portable document format
P-gp	P-glycoprotein

PI	Principal Investigator
PK	Pharmacokinetic(s)
CCI	
PT	Prothrombin time
QTcF	Corrected QT interval according to Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal (laboratory value)
US	United States (of America)
WMA	World Medical Association
β-hCG	β human chorionic gonadotropin

Note: Definitions of pharmacokinetic (PK) parameters are provided in [Section 3.8.3](#)

1. INTRODUCTION

1.1 Background

Talazoparib (also known as MDV3800, BMN 673) is a potent, orally bioavailable, small molecule poly(ADP-ribose) polymerase (PARP) inhibitor in development for the treatment of a variety of human cancers. PARP inhibitors including talazoparib exert cytotoxic effects via two mechanisms, catalytic inhibition of PARP1 and PARP2, and PARP trapping, a process in which PARP protein bound to an inhibitor does not readily dissociate from DNA, preventing DNA repair, replication, and transcription.

Talazoparib is cytotoxic to human cancer cell lines harboring gene mutations that compromise DNA repair, an effect referred to as synthetic lethality. In breast cancer MX-1 cells that are breast cancer susceptibility gene (BRCA)1-deficient, talazoparib inhibits cell growth in vitro and inhibits tumor growth and/or induces tumor regression in mouse xenografts. Antitumor activity was also demonstrated in small cell lung cancer (SCLC) cell lines and xenograft models; single-agent talazoparib reduced tumor growth to a similar extent as cisplatin in two independent SCLC xenograft models.

Nonclinical studies demonstrated increased cytotoxic effects when talazoparib was combined with certain DNA damaging chemotherapies such as alkylating agents or topoisomerase I inhibitors. Non-cytotoxic concentrations of temozolomide greatly enhanced the cytotoxic effects of talazoparib in tissue culture studies using prostate, leukemia, and Ewing sarcoma cells. Enhancement of talazoparib cytotoxic effects results from temozolomide induced cytotoxic DNA adducts that can be removed by O6 methylguanine methyltransferase (MGMT) and also potentially lethal DNA adducts that are dependent on the base excision repair (BER) response. Temozolomide induces numerous sites for PARP DNA complexes to form and become trapped by talazoparib. Similarly in an SCLC xenograft model in mice, combination treatment with talazoparib plus temozolomide resulted in a marked enhancement of antitumor effects compared with that observed with either agent alone. Tissue culture studies of talazoparib in combination with the active metabolite of irinotecan, SN38, also demonstrated enhanced pharmacologic effects of combination versus single agent treatment.

For further details on topics in this section refer to the current Investigator's Brochure (IB)¹.

1.1.1 Nonclinical Studies

The main nonclinical toxicology findings with talazoparib were early hematologic changes and subsequent bone marrow and lymphoid organ depletion, as well as focal atrophy and degeneration of testes after repeat-dose talazoparib. These findings are consistent with the exaggerated pharmacology of talazoparib and its tissue exposure pattern. The hematologic findings were generally reversible and the early hematologic changes represent sensitive and early markers of target organ toxicity.

1.1.2 Clinical Studies

As of 30 Nov 2015, approximately 319 patients with hematologic malignancies and solid tumors and 18 healthy volunteers have received talazoparib at doses up to 2 mg/day. The majority of available efficacy and safety data was obtained from studies

in solid tumors. A Phase 1 study in patients with advanced or recurrent solid tumors defined the maximum tolerated dose (MTD) of talazoparib as 1 mg/day.

1.1.2.1 Pharmacokinetics

The PK of talazoparib as a single agent was evaluated in 142 adult patients with cancer. Of these, 109 patients had solid tumors (PRP-001) and 33 had hematologic malignancies (PRP-002). Doses of 0.025 to 2 mg/day were administered orally as a single dose or as multiple doses. This range bracketed the 1 mg/day dose used in ongoing safety and efficacy studies, and provided a framework for assessing dose linearity. As the PK of talazoparib was similar in patients with solid tumors and hematologic malignancies, and no differences were apparent between males and females, the results are summarized collectively for all 142 patients.

Oral absorption of talazoparib was rapid and independent of dose after administration of single or once-daily doses. Peak talazoparib concentrations were generally achieved approximately 1 to 8 hours post-dose. Elimination appeared to follow biphasic kinetics, with a mean half-life ($T_{1/2}$) that ranged from 52.9 to 229 hours. The mean $T_{1/2}$ of talazoparib showed some evidence of decreasing with increasing dose. At 1 mg/day, the mean $T_{1/2}$ was approximately 2 days. With once daily administration, it took approximately 2 to 3 weeks to reach steady state.

The apparent volume of distribution (V/F) of talazoparib appeared to decrease with increasing dose. At 1 mg/day, the mean V/F was 415 L, or approximately 10-fold greater than total body water (42 L), which is indicative of extensive extravascular distribution². In vitro protein binding data showed that talazoparib is 78.7% bound to human plasma proteins.

No clinical studies have investigated penetration of talazoparib into the brain or cerebrospinal fluid. Talazoparib showed negligible penetration across the blood-brain barrier in rats.

Apparent total body clearance (CL/F) of talazoparib appeared to be dose linear. The mean CL/F across doses was approximately 5 L/hr. Clinical data showed that renal excretion is a major elimination pathway for unchanged parent talazoparib. Following oral administration, 44 to 90.6% of the dose was recovered in urine as unchanged parent drug over 24 hours at steady-state for doses up to 1 mg/day. Mean renal clearance ranged from 1.38 to 4.96 L/h, independent of dose, suggesting linear urinary elimination kinetics. The extent of metabolism was also minimal in nonclinical studies. Following oral administration of ^{14}C -talazoparib to rats and dogs, talazoparib was cleared primarily via excretion of unchanged parent drug and metabolized to a minor extent via oxidation and dehydrogenation. In vitro metabolism studies in human hepatic microsomes demonstrated that ^{14}C -talazoparib has high metabolic stability (> 90%) over 2 hours. A minimal extent or a lack of metabolism for ^{14}C -talazoparib was observed in the presence of freshly isolated human hepatocytes or cryopreserved human hepatocytes.

Following administration at 1 mg/day, talazoparib accumulated approximately 2.4-fold relative to a single dose. At steady state, the mean maximum observed plasma concentration (C_{max}) was 21.0 ng/mL, the mean plasma trough concentration (C_{min}) was

3.72 ng/mL, the mean area under the concentration-time curve (AUC) was 202 ng•h/mL, and the mean peak-to-trough ratio was approximately 6.

Food Effect

A food-effect study (673-103) involving administration of a single 0.5 mg dose of talazoparib to 18 healthy male subjects both under fasting conditions and with a high-fat, high-calorie meal showed that food had no effect on the extent of absorption (AUC). Food decreased the rate of absorption (C_{max} was 46% lower and T_{max} was 2.63 hours later); however this reduction in the rate of absorption following a single dose is not clinically relevant because talazoparib accumulates 2.4-fold at steady state after 1 mg once-daily dosing. Furthermore, it is thought that AUC or C_{min} drives efficacy, not C_{max} ; therefore, talazoparib can be taken with or without food. Talazoparib is being administered without regard to meals in ongoing safety and efficacy trials.

Pharmacokinetics in Special Populations

A preliminary population PK analysis was performed with data from patients in studies PRP-001 and PRP-002 to assess the effects of renal function on PK parameters of talazoparib. Talazoparib apparent systemic clearance (CL/F) in subjects with mild renal impairment (creatinine clearance [CL_{CR}], 60-89 mL/min) was similar compared with subjects with normal renal function ($CL_{CR} \geq 90$ mL/min). In subjects with moderate renal impairment (CL_{CR} , 30-59 mL/min), the talazoparib CL/F was decreased by 44%, resulting in higher talazoparib exposure. Therefore, subjects with moderate or severe renal impairment ($CL_{CR} < 60$ mL/min) may be at risk of elevated exposure ($\geq 50\%$) to talazoparib.

The effects of hepatic impairment on talazoparib PK have not been studied.

Drug-Drug Interaction

Talazoparib is unlikely to demonstrate clinically significant cytochrome P450 (CYP) inhibition- or induction-based drug-drug interactions or drug transporter inhibition-based drug-drug interactions (DDI) when co-administered with corresponding substrates. However, talazoparib is a substrate for P-glycoprotein (P-gp) and breast-cancer resistance protein (BCRP), and plasma talazoparib concentrations may increase or decrease when co-administered with P-gp or BCRP inhibitors or inducers, respectively.

Efficacy

Preliminary data demonstrated objective responses and/or clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer with deleterious germline mutations, SCLC and Ewing's sarcoma. A Phase 2 study and a Phase 3 study in patients with locally advanced or metastatic breast cancer with deleterious germline BRCA mutations are both ongoing. Efficacy data are not yet available.

The efficacy signals of talazoparib observed in the treatment of cancers with and without BRCA mutations warrant the continued development of talazoparib as a single agent at doses of 1 mg/day and support the hypothesis for enhanced cytotoxicity of talazoparib by the addition of DNA damaging agents.

Safety

The most common adverse events (AE) associated with talazoparib collected in 214 patients participating three clinical studies (PRP-001, PRP-002, and 673-201) were myelosuppression (anemia, neutropenia, thrombocytopenia), gastrointestinal toxicity (nausea, vomiting, diarrhea), and fatigue. The most common National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 AEs and serious adverse events (SAE) were associated with myelosuppression.

A total of 25 of 214 patients had SAEs that led to death (12 associated with malignancies, 3 disease progression, 2 each lung infection and pneumonia, and 1 each cardiorespiratory arrest, neutropenic sepsis, renal impairment, dyspnea, hypoxia, and respiratory failure). Of these, none was assessed as related to the study drug.

AEs leading to dose interruptions occurred in approximately 45%, 49%, and 57% of patients in company-sponsored studies PRP-002 and PRP-001, and investigator-sponsored study NCT02049593 (combination treatment), respectively. AEs leading to dose reductions occurred in approximately 6% of patients in PRP-002, more than 17% of patients in PRP-001, and more than 20% of patients in NCT02049593. Most dose modifications were due to myelosuppression.

Potential risks associated with talazoparib include hepatotoxicity, neutropenic sepsis, and febrile neutropenia.

Additional detail information can be found in the Investigational Brochure (IB).

1.2 Study Rationale

This study will investigate the DDIs between talazoparib and itraconazole and rifampin, respectively, and are compliant with the principles of the US and EU guidelines on these matters^{3,4}.

Itraconazole and rifampin are a potent inhibitor and a potent inducer of P-gp, respectively. This study will evaluate the effect of multiple doses of itraconazole or rifampin on the pharmacokinetic profile of a single dose of talazoparib in patients with advanced solid tumors. A secondary objective is to evaluate the safety and tolerability of these combinations.

1.2.1 Risk-Benefit Assessment

Talazoparib has shown clinical activity in advanced solid tumor patient populations and is being developed further as a treatment for several cancers. The adverse event profile reported indicates that talazoparib is generally well-tolerated. Myelosuppression is managed by supportive care and dose interruption and dose reduction, as necessary. Nausea and vomiting may be managed by supportive care as well. Transaminase monitoring is recommended with dose interruption or discontinuation based on the extent of transaminase elevation. Based on the cumulative safety profile and the potential benefit afforded by the mechanism of action of talazoparib, the potential benefits appear to outweigh the observed risks.

The components used as interactors for P-gp modulation are established for the purpose of DDI studies^{5,6}, and are administered at therapeutic doses following the

recommendations in their respective Summaries of Product Characteristics (SmPC) ^{7,8}. The administration is conducted within a close-observation Phase 1 unit with appropriate clinical and laboratory monitoring of relevant AEs on an inpatient basis. The ongoing development program seeks to identify tumor molecular characteristics that will identify patients more likely to derive benefit. The safety profile is acceptable in both treatment and maintenance settings.

Patients participating in this study with no clinically significant toxicities may be eligible to continue treatment on a separate open-label extension protocol after evaluation by PI and approval of Sponsor.

2. OBJECTIVES

2.1 Primary

- To separately assess the effect of P-gp inhibitor (itraconazole) and P-gp inducer (rifampin) on the single-dose PK of talazoparib in patients with advanced solid tumors.

2.2 Secondary

- To assess the safety and tolerability of a single dose of talazoparib with and without itraconazole or rifampin in patients with advanced solid tumors.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Type of Study

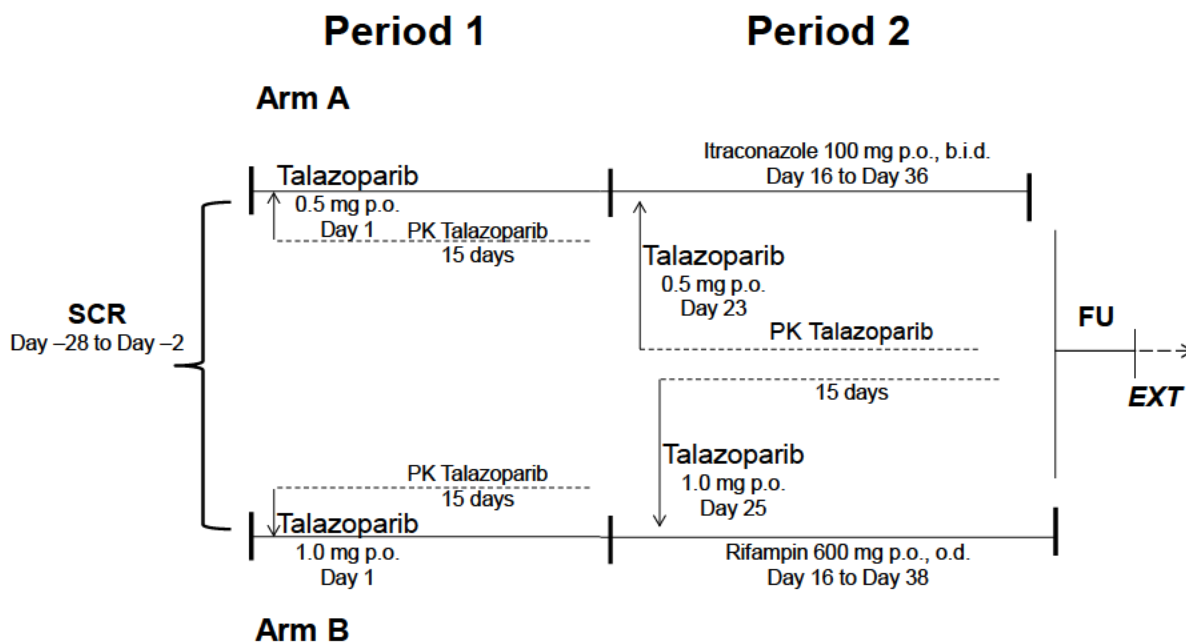
This is a Phase 1, open-label, two-armed, fixed-sequence DDI study in patients with advanced solid tumors for the investigation of the effect of P-gp inhibition and induction on the PK of talazoparib.

The main objective of this study is to evaluate the effect of multiple doses of itraconazole (used as P-gp inhibitor) or rifampin (used as P-gp inducer) on the PK profile of a single oral dose of talazoparib (0.5 mg of talazoparib alone or with itraconazole in Arm A, and 1.0 mg of talazoparib alone or with rifampin in Arm B, respectively) in patients with advanced solid tumors. A secondary objective is to evaluate the safety and tolerability of these combinations. All study subjects will be monitored for AEs throughout the study.

Each eligible subject will receive a single oral dose of 0.5 mg (Arm A) or 1 mg (Arm B) talazoparib in Period 1 (Day 1 – 15) to assess the PK of talazoparib without P-gp modulation. In Period 2, 18 subjects per study arm will receive either 100 mg oral itraconazole twice daily for 22 days (Arm A), or 600 mg oral rifampin daily for 24 days (Arm B), respectively. Subjects from the itraconazole arm (Arm A) will receive 0.5 mg talazoparib with the morning dose of the eighth day of itraconazole dosing. Likewise, subjects of the rifampin arm will receive 1.0 mg talazoparib on the tenth day of rifampin dosing ([Figure 1](#)). Itraconazole or rifampin will be taken 30 minutes before talazoparib.

Subjects participating in this study with no clinically significant toxicities may be eligible to continue talazoparib treatment on a separate extension protocol.

Figure 1 Study Design



p.o.: oral administration; b.i.d.: twice daily; o.d.: once daily; SCR: screening; FU: Follow-up; EXT: extension protocol

3.1.2 Screening Period

Subjects will sign the study-specific informed consent form (ICF) prior to any study-specific screening procedures being performed within 28 days before dosing of talazoparib on Day 1 in Period 1. The written informed consent will be obtained for all subjects, regardless of their eligibility for the study, and can be obtained in a separate visit within the screening period.

Eligibility screening will consist of the assessments as presented in the schedule of assessments (Table 1). Subjects may be enrolled if they are eligible according to the inclusion and exclusion criteria (Section 3.4). Details on the conduct of study-related assessments are given in Section 3.8.

3.1.3 Treatment Period

3.1.3.1 Baseline

Eligible subjects will enter the clinical unit on Day -1 (one day before the first administration of talazoparib). Assessments will be performed as shown in the schedule of assessments (Table 1 and Table 2) and as detailed in Section 3.8.

Once all baseline activities of Day -1 have been concluded and the eligibility criteria have been confirmed, subjects will be enrolled in Arm A or Arm B, respectively.

3.1.3.2 Period 1

In Arm A, subjects will receive 0.5 mg of oral talazoparib in the morning of Day 1. In Arm B, subjects will receive 1.0 mg of oral talazoparib in the morning of Day 1. Sampling of talazoparib for PK will be performed as shown in [Table 3](#).

Assessments of safety and tolerability will be conducted according to the schedule of assessments ([Table 1](#) and [Table 2](#)).

Subjects will be confined from Day –1 on until all study-related assessments of Day 3 have been concluded. They will present themselves on an ambulatory base for PK and safety assessments (i.e. physical examination [including weight], ECG recording, vital signs [blood pressure, heart rate, body temperature, respiratory rate]) according to the schedule of assessments ([Table 1](#) and [Table 2](#)). AEs and concomitant medication can be recorded in a subject's diary on days when no other assessments are to be performed.

3.1.3.3 Period 2

Arm A will receive 100 mg oral itraconazole twice daily, and Arm B will receive 600 mg oral rifampin daily. Both study arms will receive their interacting drug starting from Day 16 on. Dosing instructions and drug will be provided to subjects on the Day 15 visit.

In Arm A, 0.5 mg of oral talazoparib will be administered together with the morning dose of itraconazole on Day 23. Itraconazole will be taken 30 minutes before talazoparib.

In Arm B, 1.0 mg of oral talazoparib will be administered together with rifampin in the morning of Day 25. Rifampin will be taken 30 minutes before talazoparib.

In Arm A, twice daily oral administration of itraconazole will be continued until Day 36, and in Arm B, once daily administration of rifampin will be continued until Day 38. Sampling of talazoparib for PK will be performed as shown in [Table 3](#).

Subjects will be confined from Day 22 on until Day 25 for Arm A, and from Day 24 until Day 28 for Arm B. They will present themselves on an ambulatory base for PK and safety assessments according to the schedule of assessments ([Table 1](#) and [Table 2, continued](#)). AEs and concomitant medication can be recorded in a subject's diary on days when no other assessments are to be performed.

3.1.3.4 Follow-up

An ambulatory visit will be performed 20±3 days after the last dose of study drug (itraconazole or rifampin, respectively). In the event of early withdrawal of a subject, the follow-up visit should occur no sooner than 30 days after the last dose of talazoparib, unless the subject enrolls directly in the extension study. If the subject is eligible to and chooses to participate in the separate open-label extension study and the screening for the open label extension study occurs within 20±3 days after the last dose of itraconazole or rifampin, the follow up visit will not be required.

3.2 Extension Protocol

Subjects participating in this study with no clinically significant toxicities may be eligible to continue talazoparib treatment on a separate open-label extension protocol outside of this study.

3.3 Discussion of Study Design

This present study is designed according to the principles of the guidelines on DDI studies^{3,4}. The principal aim of these guidelines is to assess the concomitant medications that alter the metabolism or drug transport in individuals who receive particular dose of a drug. Such an alteration in metabolism or transport can change the exposure of a drug and potentially affect the safety and efficacy of a drug.

This clinical study will investigate the impact of itraconazole and rifampin on the PK of talazoparib. Itraconazole and rifampin are known agents which inhibit and induce the intestinal P-gp transport^{5,6}, respectively. Talazoparib is a substrate for P-gp¹ and its exposure as well as its elimination may be influenced by compounds which affect the intestinal P-gp transport, and thus may alter the safety and efficacy of talazoparib.

3.4 Selection of Study Population

The study is planned to enroll a total of 36 patients with advanced solid cancer in order to have 18 participants per study arm.

3.4.1 Inclusion Criteria

Each subject eligible to participate in this study must meet all of the following criteria:

1. Arm A: At least 18 years of age and <65 years of age (at the time point of consent) and willing and able to provide informed consent.
Arm B: At least 18 years of age (at the time point of consent) and willing and able to provide informed consent.
2. Histologically confirmed advanced solid tumor judged by the Investigator to not be appropriate for standard therapy.
3. ECOG performance status ≤ 2 at screening and at time of enrollment.
4. Expected life expectancy of ≥ 3 months.
5. Able to swallow the study drug and comply with study requirements.
6. Female subjects may be enrolled if they are
 - a. considered not of childbearing potential including those who are surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy ≥ 6 months before enrollment, with documentation of the procedure) or who are post-menopausal, defined as:
 - ≥ 55 years of age with no spontaneous menses for ≥ 12 months before Day -1
 - < 55 years of age with no spontaneous menses for ≥ 12 months before Day -1 and with a postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/L (or meeting criteria for post-menopausal status by the local laboratory)

or

b.

Arm A:

of childbearing potential but having a negative serum pregnancy test at Screening and Day -1 **AND** also using a highly effective form of contraception from screening or at least 21 days prior to study drug administration (whichever is earlier) until 45 days after last intake of study medication, and defined as:

- Placement of an intrauterine device
- Sexual partner(s) vasectomized for ≥ 6 months before enrollment
- Sexual abstinence when in relation to the preferred and usual lifestyle of the subject

Arm B:

of childbearing potential but having a negative serum pregnancy test at Screening and Day -1 **AND** also using a highly effective form of contraception from screening or at least 21 days prior to study drug administration (whichever is earlier) until 45 days after last intake of study medication, defined as at least one of the following:

- Established use of an oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
- Established use of an oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
- Placement of an intrauterine device or intrauterine hormone-releasing system
- Must also use a double-barrier method (e.g. condom or diaphragm plus spermicide) together with one of the 3 contraceptive methods listed above.
- Sexual partner(s) vasectomized for ≥ 6 months before enrollment
- Sexual abstinence when in relation to the preferred and usual lifestyle of the subject

and

- c. do not donate eggs from the time point of investigational medicinal product (IMP) administration until at least 45 days thereafter.

7. Males with partners of childbearing potential may be enrolled if they

- a. use a condom when having sex with a pregnant woman or with a woman of childbearing potential from 21 days before the first dose of study drug through 105 days after last dose of study drug. Contraception should be considered for a non-pregnant female partner of childbearing potential.

and

- b. do not donate sperm from the time point of study drug administration until at least 105 days thereafter.

8. Female subjects must not be breastfeeding at screening and during the study

participation until 45 days after the last dose of the study drug.

9. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.

3.4.2 Exclusion Criteria

Each subject eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. Treatment within 14 days or 5 half lives prior to dosing with any type of systemic anticancer therapy or any investigational agent, whichever is longer
2. Major surgery within 8 weeks before screening.
3. Serious accompanying disorder or impaired organ function, including the following:
 - a. Cardiac:
 - Myocardial infarction or symptomatic cardiac ischemia within 6 months before screening.
 - Arm A: Heart failure of severity grade class II, III or IV according to New York Heart Association (NYHA) within 6 months of enrollment.
 - Arm B: Heart failure of severity grade class III or IV according to NYHA within 3 months of enrollment.
 - Clinically significant cardiac arrhythmias if not adequately treated or controlled (e.g. by medication, or pacemaker).
 - History of Mobitz II second degree or third degree heart block unless a permanent pacemaker is in place.
 - Hypotension as indicated by systolic blood pressure < 86 mm Hg at screening or Day -1. May be repeated in 15 minutes if initial reading is believed to be atypical for the subject.
 - Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG).
 - poorly controlled hypertension as indicated by systolic blood pressure > 175 mm Hg or diastolic blood pressure > 105 mm Hg at screening. May be repeated in 15 minutes if initial reading is believed to be atypical for the subject.
 - Screening QTcF \geq 450 ms in males or \geq 480 ms in females.
 - b. Renal: eGFR (estimated glomerular filtration rate) \leq 50 mL/min/1.73 m² by the MDRD equation (Modification of Diet in Renal Disease [available via www.mdrd.com]) at screening and Day -1.
 - c. Total serum bilirubin > 1.5 times ULN (> 3 times ULN for subjects with Gilbert's syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation)
 - d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) \geq 2.5 times ULN
 - e. Arm A: History of clinically significant liver injury or other adverse reaction to azole antifungals; Arm B: History of clinically significant liver injury or other adverse reaction to rifampin, rifamycin or other rifamycin derivatives.

- f. Bone marrow reserve: neutrophils < 1500/ μ L, platelets < 100,000/ μ L, or hemoglobin < 9 g/dL (blood samples collected after \geq 14 days without growth factor support or transfusion).
 - g. Albumin < 3.0 g/dL.
4. Symptomatic or impending spinal cord compression or cauda equina syndrome.
 5. Non-healing wound, ulcer, or bone fracture, not including a pathological bone fracture caused by a pre-existent pathological bone lesion.
 6. Known myelodysplastic syndrome.
 7. Subjects with the following serologies should be excluded: HBsAg+ or anti-HBc+; HCV+; HIV+.
 8. Serious or unstable medical condition that interferes with ability to tolerate treatment or assessments associated with the protocol.
 9. Gastrointestinal disorder affecting absorption.
 10. Known hypersensitivity to any of the talazoparib capsule components.
 11. Co-administration of the following drugs (including alimentary supplements and herbal medicines, if applicable, within 7 days or 5 half-lives before Day 1, whichever is longer, until end of Period 2; with exception of intake of itraconazole in Arm A and rifampin in Arm B as per study design):

- Arm A:

Use of a strong P-gp inhibitor (e.g., dronedarone, quinidine, ranolazine, verapamil, itraconazole, ketoconazole), strong P-gp inducer (e.g. rifampin, tipranavir, ritonavir), CYP3A4 substrates (see P450 Drug Interaction Table of DMIU: <http://medicine.iupui.edu/clinpharm/ddis/main-table/>), or strong inhibitor of BCRP (e.g., elacridar [GF120918]). Subjects must also abstain from the use of any other prescription or nonprescription drugs or supplements with potential P-glycoprotein (P-gp) and BCRP interaction. Refer to the following website for a complete list: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inhibitors>.

Contra-indicated drugs from the itraconazole label: methadone, disopyramide, dofetilide, ergot alkaloids (such as dihydroergotamine, ergometrine [ergonovine], ergotamine, methylethergometrine [methylethergonovine]), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, nisoldipine, felodipine, ranolazine, eplerenone and cisapride.

- Arm B:

Use of a strong P-gp inhibitor (e.g., dronedarone, quinidine, ranolazine, verapamil, itraconazole, ketoconazole), strong P-gp inducer (e.g. rifampin, tipranavir, ritonavir), CYP3A4 substrates (see P450 Drug Interaction Table of DMIU: <http://medicine.iupui.edu/clinpharm/ddis/main-table/>), or strong inhibitor of BCRP (e.g., elacridar [GF120918]). Subjects must also abstain from the use of any other prescription or nonprescription drugs or supplements with potential P-glycoprotein (P-gp) and BCRP interaction. Refer to the following website for a complete list: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inhibitors>.

Contra-indicated drugs from the rifampin label: protease inhibitors (e.g. amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, tipranavir and saquinavir – with and without ritonavir), broad-spectrum tri-azole antifungal agent (e.g. itraconazole, voriconazole), potentially hepatotoxic narcotic agent (e.g. halothane).

12. Any condition or reason that interferes with ability to participate in the study, causes undue risk, or complicates the interpretation of safety data, in the opinion of the Investigator or Sponsor (e.g. non-compliance, excessive alcohol consumption, intake of drugs of abuse unless these drugs are medically indicated [e.g. opiates for pain relief]).

3.5 Removal of Subjects from Therapy or Assessment

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason.

The Investigator has the right to terminate participation of a subject for any of the following reasons:

- Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Intolerable toxicity as evidenced by the occurrence of severe AEs, or SAEs
- Non-compliance that is likely to affect the validity of the data obtained from the subject.

If a subject withdraws or is removed from further study participation, the follow-up visit will be conducted as described in [Section 3.1.3.4](#). In the event of early withdrawal, the follow-up visit should not take place sooner than 30 days after the last dose of talazoparib, unless the subject enrolls directly in the extension study, in which case the follow-up may occur earlier.

If a subject is withdrawn from the study, the Sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

The decision regarding the replacement of subjects will be documented.

The Investigator will make every effort to ensure that non-completers and dropouts who have received study drug complete the safety follow-up assessments.

3.6 Premature Discontinuation of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, e.g., due to:
 - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
 - Other unfavorable safety findings.
- Sponsor's decision.

- Poor enrollment rate of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's IMP.

Health authorities and IECs (Independent Ethics Committees) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of health authorities.

3.7 Treatments

3.7.1 Treatments Administered

Subjects will receive single oral doses of 0.5 mg talazoparib each on Day 1 and Day 23 for Arm A, or single doses of 1 mg talazoparib on Day 1 and Day 25 for Arm B.

3.7.2 Identity of Investigational Products

For details concerning drug storage and drug accountability see [Appendix 8.1](#).

3.7.2.1 Substrate

Active substance: Talazoparib, CCI [REDACTED]

Indication: Advanced solid tumors

Dosage form: capsule for oral administration

Strength: 0.25 mg, 1.0 mg

Dose: Arm A: 2 single doses, each of 0.5 mg talazoparib (2 capsules of 0.25 mg)
Arm B: 2 single doses, each of 1.0 mg talazoparib (1 capsule of 1.0 mg)

3.7.2.2 Interactors

Itraconazole (P-gp Inhibitor)

Active substance: Itraconazole
ATC code J02AC02.

Indication: Fungal infections

Dosage form: capsule/tablet for oral administration

Strength: 100 mg

Dose: 100 mg itraconazole, twice daily, for 21 days

Rifampin (P-gp Inducer)

Active substance: Rifampin
ATC code J04AB02

Indication: Microbial infections (esp. tuberculosis and leprosy)

Dosage form: capsule/tablet for oral administration

Strength: 300 mg

Dose: 600 mg rifampin, once daily, for 23 days

3.7.3 Treatment Assignment

After obtaining informed consent, subjects will be screened according to the inclusion and exclusion criteria. Enrolled subjects will receive a unique subject number (01 to 36) prior to dosing. The subject number will ensure identification throughout the study. Replacement subjects will receive the number of the subject to be replaced, increased by 100 (e.g. 101 replacement number for subject number 01), and will be administered the same treatment.

After enrollment, subjects will be assigned to Arm A or Arm B of the study based on meeting the respective eligibility criteria and investigator decision.

Subjects who drop out or withdraw for any reason without completing all screening evaluations successfully, will be considered as “screening failures”. The Investigator or authorized designee will keep a screening log of all subjects screened in order to assess the numbers and characteristics of the excluded subjects, and the reasons for their exclusion.

3.7.4 Selection of Doses in the Study

The dose of 0.5 mg talazoparib is 50% of MTD for daily administration. The reduction of the MTD is aimed to increase the safety margin when itraconazole is administered in Arm A, as the interacting drug may increase the exposure of talazoparib. For Arm B, 1.0 mg of talazoparib will be administered which is the recommended daily dose for the treatment of solid tumors as a single-agent therapy. As it is expected that rifampin may reduce the exposure of talazoparib. No general safety issues are expected.

Refer to the IB¹ (Section 6.1) for most recent guidance on the formulation, dosage and administration of talazoparib.

The doses of itraconazole and rifampin were selected following the dosing recommendations for their use as antifungal and antimicrobial agent, in the respective SmPCs ^{7,8}.

3.7.5 Timing of Doses in the Study

In Period 1, talazoparib will be administered without the interacting drugs in the morning of Day 1 under fasted conditions (8 hours before until 2 hours after dosing).

In Period 2, talazoparib will be administered in combination with the interacting drugs in the morning of Day 23 (itraconazole), and of Day 25 (rifampin) under fasted conditions (8 hours before until 2 hours after dosing). On these days, itraconazole or rifampin will be taken 30 minutes before talazoparib.

Itraconazole will be administered twice daily, once in the morning and once in the evening (approximately 12 hours apart) from Day 16 to Day 22 and from Day 23 to Day 36 in Period 2 immediately after the meal (breakfast and dinner, respectively).

Rifampin will be administered once daily in the morning from Day 16 to Day 24 and from Day 26 to Day 38 in Period 2 at least 30 minutes before breakfast.

3.7.6 Meals During the Study

Subjects will be required to be fasting overnight from at least 8 hours before until at least 2 hour after the administration of talazoparib. Within this food-restricted period the consumption of water is allowed. Grapefruit juice is prohibited at least 24 hours prior to dosing of talazoparib on Days 1 and 23 until 24 hours after dose.

According to the respective SmPCs^{7,8}, itraconazole should be administered immediately after the meal, and rifampin should be administered at least 30 minutes before a meal in order to achieve optimum intestinal absorption. In case of concomitant administration with talazoparib, the interactors must be administered following the fasting restrictions of talazoparib on Days 23 and 25, respectively.

3.7.7 Blinding

Not applicable. This is an uncontrolled, open-label clinical study.

3.7.8 Concomitant Medication and Other Restrictions During the Study

Any concomitant medication will be administered under supervision of the medical staff of the unit during the in-house period. On days when talazoparib, itraconazole or rifampin is administered, any concomitant medication (including H2-blockers [cimetidine, ranitidine, famotidine etc.], PPIs [omeprazole, pantoprazole etc.], and anti-acids) will be administered at least 2 hours thereafter.

The use of warfarin is allowed with careful monitoring of international normalized ratio (INR) and the dose can be adjusted as needed.

For statins which are CYP3A4 substrates, using with itraconazole might increase the plasma concentration of statins. Careful monitoring is recommended and the dose can be adjusted as needed.

Patients on verapamil are excluded from the study unless the subject and Investigator agree to switch to an alternative, allowed antihypertensive. Any such switch must begin at least 7 days before Day 1 and additional blood pressure monitoring will be performed as considered medically necessary by the investigator to monitor blood pressure control. The patient should be switched back to verapamil after the last PK sample is taken, again with appropriate blood pressure monitoring, unless medically contraindicated in the opinion of the investigator.

3.7.9 Treatment Compliance

Talazoparib will be administered orally under supervision of the Investigator or his/her designee. Compliance will be confirmed by bioanalytical assessment of the IMP in blood samples.

The exact times of study drug administration and the number of units administered will be recorded in the eCRF.

The administration of itraconazole and rifampin will be supervised by the Investigator on days when co-administration with talazoparib occurs. On all other days, the subjects will self-administer these drugs and record the dose, the time and date of the intake in a diary.

3.8 Pharmacokinetic, Efficacy and Safety Measurements and Variables

3.8.1 Pharmacokinetic, Efficacy and Safety Measurements Assessed

3.8.1.1 Pharmacokinetic Measurements

For PK of talazoparib blood samples will be taken as outlined in the PK sampling schedule ([Table 3](#)). The exact times of each blood collection will be recorded in the eCRF.

The details of sample acquisition, processing, storage and shipment will be issued in a laboratory manual.

3.8.1.2 Efficacy Measurements

No efficacy analysis is planned in this study, although baseline tumor assessments will be obtained in the event that eligible subjects choose to continue talazoparib treatment on a separate extension protocol.

3.8.1.3 Safety Measurements

Safety and tolerability assessments will consist of AEs, clinical laboratory, vital signs, 12-lead ECG, and physical examination. Assessments will be performed in accordance with the schedules of assessments ([Table 1](#) and [Table 2](#)).

3.8.1.3.1 Adverse Events

Adverse events will be recorded following the first dose of study drug (Day 1) until completion of the follow-up visit. SAE will be collected from the time the subjects signs Informed Consents until completion of the follow-up visit. AEs which are still active at the conclusion of the follow-up visit will be monitored until resolution, or as deemed necessary by the Investigator or Sponsor. Any clinically significant observations in results of clinical laboratory, 12-lead ECGs, vital signs or physical examinations will be recorded as AEs.

A treatment-emergent AE (TEAE) is defined as any event not present prior to administration of the study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.

An AE which occurs prior to (the first) administration of the talazoparib will be considered a pre-treatment AE and documented on the medical history eCRF.

At several time points before and after drug administration, subjects will be asked non-leading questions to determine the occurrence of AEs. Subjects will be asked in general terms about any AEs at regular intervals during the study. In addition, all AEs reported spontaneously during the course of the study will be recorded. Events that meet serious criteria will be reported as detailed in Appendix 8.2.

All answers will be coded by the Investigator using the Medical Dictionary for Regulatory Activities (MedDRA; most recent version) [for AEs](#) and will be recorded in the AEs Record. Details on the rating of the severity of the AEs and relationship to the study treatment are given in Appendix 8.2.

Pregnancy of female subjects and female partners of male subjects will be monitored along with follow-up, if warranted (see also [Appendix 8.3](#)).

3.8.1.3.2 Eastern Co-Operative Oncology Group Performance Status (ECOG)

The performance status will be determined according to the ECOG Performance Status scale¹⁰:

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

3.8.1.3.3 Clinical Laboratory

The below listed tests will be performed by the local laboratory at time points indicated in the Schedules of Assessments ([Table 1](#) and [Table 2](#)) and before dosing, if applicable (talazoparib, as well as itraconazole and/or rifampin, respectively).

Clinical Laboratory Tests			
Hematology and Coagulation	Serum Chemistry	Urinalysis	Additional Tests
Hemoglobin	Sodium	pH	<u>Serology</u> : anti-HIV-1/2, HbsAg and anti-HBc, HCV
Hematocrit	Potassium	Specific gravity	
Erythrocytes	Chloride	Color	<u>FSH test</u> Collect only for females with no spontaneous menses for ≥12 months, who are <55 years old, and who do not have documented surgical sterilization
Platelets	Calcium	Protein	
Leukocytes	Inorganic phosphate	Glucose	<u>Serum pregnancy test</u> (β-hCG) for women of childbearing potential, including women whose last menstruation was less than 1 year before screening
Neutrophils	Urea	Ketones	
Eosinophils	Creatinine (including calculation eGFR)	Hemoglobin (erythrocytes)	<u>Urine drugs of abuse test</u> including but not limited to cannabinoids, amphetamines, methamphetamines, opiates, methadone,
Lymphocytes			
Monocytes	Total bilirubin	Leukocytes	
Basophils	Direct bilirubin [§]	Microscopic analysis, if urine is positive for protein, leukocytes or hemoglobin	
INR*	ALT		
aPTT*	AST		
PT*	GGT		
	ALP		
	LDH		
	CPK		
	Triglycerides*		
	Total cholesterol*		

Clinical Laboratory Tests			
Hematology and Coagulation	Serum Chemistry	Urinalysis	Additional Tests
	Total protein* Albumin*		cocaine, benzodiazepines, and barbiturates
	Glucose		Alcohol breath test.

* At screening only

§ Direct bilirubin will be measured only if total bilirubin is higher than upper limit of normal range

The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate the clinical significance according to the applicable **CCI**. Detailed information about follow-up of abnormal laboratory results is given in [Appendix 8.2.2.2](#).

3.8.1.3.4 Vital Signs

Systolic and diastolic blood pressure and heart rate will be recorded in supine position after the subject has been resting for at least 5 minutes in a supine position. These assessments will be made using an automated device. Body temperature and respiratory rate will be measured subsequently.

3.8.1.3.5 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has been resting for at least 5 minutes in a supine position. Triplicate ECG recordings will be performed 1 to 2 minutes apart. For the timing of the different types of ECG recordings refer to the schedules of assessments ([Table 1](#) and [Table 2](#)).

The 12 lead ECGs will be recorded using an ECG machine equipped with computer based interval measurements. The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, corrected QT interval according to Fridericia's formula (QTcF) and the interpretation of the ECG profile by the Investigator. For any visit and the time point with ECG and PK assessments, ECG will be taken 15 minutes before PK sampling.

3.8.1.3.6 Physical Examination

A complete physical examination will be performed consisting of all body systems (with the exception of genitalia, anus/rectal, and breast examinations, which will only be performed if medically indicated). Unscheduled symptom-directed physical examinations may be conducted at any time per the Investigator's discretion.

3.8.1.4 Total of Blood Volume

During the course of this clinical study, a maximum volume of approximately 250 mL blood will be collected for PK and safety assessments.

If deemed necessary by the Investigator, additional blood samples for safety or PK analysis may be taken at additional (unscheduled) and follow-up visit(s) up to an additional volume of 30 mL.

3.8.2 Appropriateness of Measurements

The assessments, which will be made in this study are standard for DDI studies, and generally recognized as reliable, accurate and relevant.

3.8.2.1 Timing of Assessments

For PK, pre-dose samples will be obtained between waking up and dosing. Post-dose samples up to 60 minutes post-dose will be obtained with a time window of ± 1 minute. From after 60 minutes until 12 hours post-dose, samples will be obtained with time margins of ± 10 minutes. Thereafter, samples should be obtained within ± 30 minutes of the scheduled time points.

For safety, pre-dose assessments will be performed between waking up and dosing. Post-dose assessments will be performed with time margins of ± 60 minutes of the planned scheme time.

In the event assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that PK blood sampling will be done after the ECG and vital signs recordings have been conducted, with blood sampling exactly on time.

3.8.3 Pharmacokinetic, Efficacy and Safety Variables

3.8.3.1 Pharmacokinetic Parameters

The following PK parameters will be calculated as data allows for talazoparib concentrations in plasma. PK variables will be computed using WinNonlin Professional or another appropriate software. As appropriate, additional PK parameters may be calculated and reported. A complete list of PK parameters will be provided in the Statistical Analysis Plan (SAP).

C_{\max}	Maximum observed plasma concentration
T_{\max}	Time to attain maximum observed plasma concentration
$AUC_{0-\text{last}}$	Area under the plasma concentration-time curve up to time t, where t is the last time point with concentrations above the lower limit of quantitation (LLOQ)
$AUC_{0-\text{inf}}$	Area under the plasma concentration-time curve from time 0 to infinity calculated as: $AUC_{0-\text{inf}} = AUC_{0-t} + C_{\text{last}}/k_{\text{el}}$, where C_{last} is the last measurable plasma concentration
k_{el}	Terminal elimination rate constant
$T_{1/2}$	Terminal elimination half-life, calculated as $0.693/k_{\text{el}}$
CL/F	Apparent Clearance
V_d/F	Volume of distribution at terminal phase

PK parameters derived from metabolite profiling will be evaluated if applicable.

3.8.3.2 Efficacy Variable(s)

Not applicable.

3.8.3.3 Safety Variables

The safety variables to be measured include but are not limited to the variables as given below. A complete list of safety variables will be provided in the SAP.

- AEs
- Clinical laboratory
- Vital signs
- ECG
- Physical examination

3.8.4 Drug Concentration Measurements

Talazoparib will be analyzed using a validated LC-MS/MS method.

3.9 Statistical Procedures and Determination of Sample Size

3.9.1 Analysis Populations

3.9.1.1 Safety Population

All subjects who have received at least one dose of talazoparib.

3.9.1.2 Pharmacokinetic Population

- PK population: All subjects who have received any dose of talazoparib and have 1 reportable concentration data.
- PK analysis population: All subjects who have receive 2 doses of talazoparib in Periods 1 and 2, and provide sufficient bioanalytical assessments to calculate reliable estimates of the PK parameters.

3.9.2 Statistical and Analytical Plan for Pharmacokinetic and Safety Evaluation

An SAP will be generated by the Biostatistics Department of CCI; the SAP will be finalized prior to database lock. Full details of the analysis to be performed will be included in the SAP.

Any deviation from the SAP will be reported in the Section “Changes in Planned Analysis” in the Clinical Study Report.

3.9.2.1 Demographic and Other Baseline Characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using MedDRA terms.

3.9.2.2 Pharmacokinetic Evaluation

The concentration-times data of talazoparib in plasma will be separately tabulated by treatment arm

The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms), geometric

CV, minimum, median, maximum value and the number of measurements. Concentrations below LLOQ will be set to zero when calculating descriptive statistics. Means at any time will only be reported if the mean \geq LLOQ; for mean $<$ LLOQ, “missing” is reported in the tables. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

The PK characteristics of T_{\max} will be described utilizing minimum, maximum and median. In calculation of PK parameters, pre-dose concentrations $<$ LLOQ are set to zero; all post-dose concentrations $<$ LLOQ are set as missing value.

Statistical analyses will be performed to assess the effect of steady-state itraconazole and rifampin on the PK of talazoparib using the treatment in combination with talazoparib as Test and the treatment with talazoparib alone as Reference. Only subjects with data for both Reference and Test treatments will be included in the analysis. A linear mixed effects model that includes treatment as a fixed factor and subjects nested within the sequence as a random factor will be fitted to the log transformed PK parameters ($AUC_{0-\infty}$, $AUC_{0-\text{last}}$ and C_{\max}). A point estimate and the corresponding 90% CI for the difference between least squares means of Test and Reference treatment (Test – Reference) will be calculated. The antilogarithm of this value will be calculated to obtain the point estimate and the 90% CI for the ratio (Test/Reference) of the geometric means on the untransformed scale.

3.9.2.3 Evaluation of Safety and Tolerability

All safety analyses will be performed using the safety population. Safety will be evaluated using summaries of adverse events, physical evaluation (and weight), vital signs, electrocardiograms (ECGs), and laboratory evaluations.

3.9.2.3.1 Adverse Events

Adverse events will be coded to preferred term and system organ class using MedDRA and classified by severity using NCI CTCAE. The number and percentage of subjects with AEs will be presented by MedDRA system organ class and preferred term, relationship to study treatment, severity, seriousness, and outcome (e.g. leading to permanent treatment discontinuation).

3.9.2.3.2 Clinical Laboratory

Clinical laboratory data will be listed accompanied by an indication if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

Laboratory values will be classified by severity using NCI CTCAE. Change from baseline in laboratory values will be tabulated and summarized graphically.

3.9.2.3.3 Vital Signs and Electrocardiograms

Vital signs and ECG parameters will be listed and they will be presented descriptively, where applicable.

3.9.2.3.4 Physical Examination

Clinically relevant changes of physical examination findings from baseline will be qualified as AEs.

3.9.3 Determination of Sample Size

Based on the population PK analysis, the intra-subject variability was estimated to be 42% in terms of percent coefficient of variation (%CV). With a sample size of 15 evaluable subjects, the precision or half width of 90% CI for Test Reference comparison on a log scale will be 0.259 from the observed difference in means. This calculation is based on an analysis of variance (ANOVA) model including effects of treatment and subjects nested within the sequence. When the true ratio is 1, the equivalence limits are 0.77 and 1.30. Eighteen subjects will be enrolled in each treatment group to allow for 15% of incompleteness or loss to follow up. Subjects who discontinue prior to completion of both periods may be replaced upon agreement of the Investigator and the Sponsor.

3.10 Data Quality Assurance

The study may be audited to assess adherence to the Clinical Study Protocol (CSP) and Quality System. During the conduct of the study, process-related audits may be performed as well. An audit certificate will be provided in the appendices of the final Clinical Study Report (CSR) outlining the audit performed and other related activities.

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study will be conducted according to the relevant regulatory requirements. eCRF entries will be verified with the source documentation, if applicable.

Regulatory authorities, the IEC and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed at **CCI** for all documents that are generated in relation with the study.

An explanation will be given for all missing, unused and spurious data in the relevant sections of the CSR.

4. ETHICS

4.1 Independent Ethics Committee

Prior to commencement of the study, the protocol, any amendments, subject information and ICF, any other written information to be provided to the subject, subject recruitment procedures, if any, IB, information about payments and compensation available to subjects, if not mentioned in the subject information, the Investigator's current curriculum vitae and/or other documentation evidencing qualifications, and other documents as required by the regulatory authorities and IEC will be submitted. The submission letter will clearly identify (by study identification number, including version, EudraCT no., title and/or date of the document) which documents have been submitted. Written approval/favorable opinion must be obtained from regulatory authorities/IEC prior to commencement of the study.

During the study, the Investigator must promptly in accordance with local requirements report the following to the IEC (central or local IEC, as applicable): updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial amendments to the protocol, non-substantial amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the study status and other documents as required by the local IEC.

Substantial amendments must not be implemented before approval/favorable opinion of the IEC, unless necessary to eliminate hazards to the subjects.

The Investigator must maintain an accurate and complete record of all submissions made to the IEC. The records should be filed in the Investigator's study file and copies must be sent to the Sponsor.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments¹¹.

This study is also designed to comply with ICH E6 Guideline for GCP (ICH Harmonised Tripartite Guideline, E6: Guideline for Good Clinical Practice [CPMP/ICH/135/95], Jan, 1997)¹², the EU Clinical Trial Directive 2001/20/EC (Directive of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct, 4th April 2001)¹³, Commission Directive 2005/28/EC¹⁴ and the applicable regulatory requirements.

ICH adopted guidelines and other relevant international guidelines, recommendations and requirements will be taken into account as comprehensively as possible, as long as they do not violate local law.

The Investigator will be responsible for the care of the subjects throughout the study. If the Investigator is not present in the clinical site, he/she will leave instructions for the staff and a telephone number where he/she can be reached.

The Investigator will be responsible for the medical follow up of the subjects.

4.3 Subject Information and Consent

All subjects will be informed verbally and in writing regarding the objectives, procedures and risks of study participation in local language. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

The ICF contains information about the objectives of the study, about the procedures followed during the study and about the risks and restrictions of the study, with special reference to possible side effects of the medication and potential interactions. In addition, insurance coverage provided during the study is explained. The subjects will have to sign the ICF before any study related procedures are started.

Additionally, the process of obtaining informed consent should be documented in the subject's source documents.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC, and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

The elements addressed in the ICF are according to the ICH E6 Guideline for GCP (CPMP/ICH/135/95) ¹².

4.4 Privacy

All personal details will be treated as confidential by the Investigator and involved site **CCI** and handling of personal data will be in compliance with the local data protection and privacy regulations.

The Investigator will particularly pay attention that source documents or additional documents handed over to the Sponsor obscure subject names and other confidential personal details, as per local regulations.

5. STUDY ADMINISTRATIVE STRUCTURE

5.1 Distribution of Activities

Preparation of study drug

The study drug will be prepared at the site or the site pharmacy according to local regulations.

Laboratory assessments

The analysis of talazoparib in plasma samples will be performed at the PPD [REDACTED] USA.

The analysis of clinical laboratory samples will be performed at the local safety laboratory as detailed in the laboratory manual.

The design of the eCRF will be prepared with the computer program Oracle Clinical (Oracle, Redwood Shores, Redwood City, CA, USA) by the Database Programming Department of CCI [REDACTED]

Data management

Data management will be performed with the computer programs Oracle Clinical (Oracle, Redwood Shores, Redwood City, CA, USA), SAS for Windows® (SAS Institute Inc., Cary, NC, USA) and [REDACTED] CCI [REDACTED] [REDACTED].

Statistics

An SAP will be provided by the Biostatistics Department of CCI [REDACTED]. The safety analysis and the statistical evaluation of PK and PD parameters will be conducted by the Biostatistics Department of CCI [REDACTED]. Non-compartmental analyses (NCA) will be performed with WinNonlin™ Professional, Version 6.3 or higher. Statistical analysis will be performed with the computer program SAS for Windows® (SAS Institute Inc., Cary, NC, USA).

CSR writing

The CSR, structured in accordance with the guideline 'Structure and Content of Clinical Study Reports - ICH E3¹⁵', will be written by CCI [REDACTED]

5.2 Documentation

5.2.1 Archiving

All documents concerning the study will be kept on file in the Central Archives of CCI [REDACTED] for at least 15 years after conduct of the study. The Sponsor will receive the completed eCRFs (upon request, as PDF file).

5.2.2 Recording of Data in Source Documents and CRFs

All data will be recorded as source data first and entered later into the eCRF. A Data Management Plan will be written by the Data Management Department of CCI [REDACTED] which will be finalized prior to performing any data validation.

6. CONFIDENTIALITY AND PUBLICATION POLICY

By signing this CSP, the Investigator reaffirms to the Sponsor that he/she will maintain in confidence all information furnished to him/her, or resulting from this study. He/She will only divulge such information as may be necessary to the IEC and the members of the staff and the subjects who are involved in this study.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and CCI

7. REFERENCES

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14. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
15. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95), Nov 1995
16. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Note for Guidance on Clinical Safety Data Management, June 1995
17. Common Terminology Criteria for Adverse Events v4.0 (CTCAE), US department of Health and Human Services, National Institutes of Health, National Cancer Institute 2009

8. APPENDICES

8.1 Drug Accountability

Upon receipt of the study drug, it will be inspected and counted by the Investigator or the responsible pharmacist. If necessary, the study drug will be re-packed per dosing occasion, and labeled according to local regulatory requirements.

The study drug will be kept at the local pharmacy or at the site in a locked and secured storage facility accessible only to those authorized by the Investigator to dispense the study drug.

The responsible pharmacist will keep an inventory. This will include the quantity of study drug received for the study and a record of what is dispensed, to whom and when.

On termination of the study the Investigator or delegate will conduct a final inventory of the study drug supply and will record the results of this inventory in the Drug Accountability Form. Unused study drug will be returned to the Sponsor at the end of the study or will be locally destroyed according to **CCI** standard procedures.

8.2 (Serious) Adverse Events Evaluation and Reporting

The safety management of this study will comply with all applicable national and international regulatory requirements and adhere to the full requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, October, 1994)¹⁶.

8.2.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE definitions will be followed as stated in the 'Note for Guidance on clinical safety data management: definitions and standards for expedited reporting' (ICH topic E2A)¹⁶.

Serious adverse events will be collected from the time the subject signs Informed Consent until completion of the follow-up visit. Non-serious adverse events will be collected from the time the subject receives first dose of study drug.

The Investigator will report in the eCRF all AEs observed, spontaneously reported or noted (verbally or e.g. in a diary) by subjects. In addition, trial subjects will be questioned by site personnel about AEs at regular intervals using standard non-leading questions, such as "have you experienced anything new or different since your previous study visit?"

Grading of severity, clinical significance, causality and seriousness will be determined by the Investigator using the CTCAE scale and will be reported in the eCRF.

8.2.2 Grading of Severity

The severity of AEs will be graded using the most current version of the NCI TCAE 5-point scale¹⁷:

- **Mild (Grade 1):** Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2):** Minimal, local or non-invasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL). Intervention may or may not be indicated.
- **Severe (Grade 3):** Medically significant but not necessarily life-threatening; severe is not the same as serious; determination of serious vs. life-threatening will be based upon subject's condition / anticipated outcome, e.g. serious is usually reserved for an event which poses an immediate threat to subject's life or could pose a threat to subject's life if not treated promptly
- **Life-threatening (Grade 4):** Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)** related to AE.

It is emphasized that the term severe is a measure of severity: thus a severe AE is not necessarily "serious" as per regulatory definition. For example, itching for several days may be rated as severe, but may not meet regulatory definition of 'serious' (Section 8.2.3).

8.2.2.1 Grading of Relationship (Causality)

The relationship of any AE to the study drug will be assessed and graded as probable, possible or not related as following:

Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable, and/or in which other drugs, chemicals, or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

8.2.2.2 Test results and physical examination findings

Test findings and physical examination findings can result in AEs if they are:

- Associated with accompanying symptoms
- Requires additional diagnostic testing or medical/surgical intervention, and /

- Leads to a change in study dosing or discontinuation of the study medication; results in the addition of significant additional concomitant drug treatment or other therapy
- Leads to any of the outcomes included in the definition of a SAE
- Is considered to be an AE by the Investigator

Reporting an AE should not be triggered by:

- Merely needing to repeat an abnormal test, or,
- Any abnormal test result that is determined to be an error, e.g. it is not reproducible or sustainable on repeat.

8.2.3 Serious Adverse Events

An SAE is any untoward medical occurrence that, on the basis of medical and scientific judgment:

- **Results in death**
- **Is life-threatening** (This refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- **Requires inpatient hospitalization** for a medical reason or prolongation of existing hospitalization (This refers to hospital admission required for treatment of the AE).

Note: this does not include confinement in, for example, a respite unit; a skilled nursing unit; rehabilitation facility; the clinical research unit; or confinement due to planned reason, unrelated to study participation.

- **Results in persistent or significant disability/incapacity**
- **Is a congenital anomaly/birth defect**

Any other situation, such as an important medical event that is considered by the Investigator to be serious but that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. Examples of such events include but are not limited to intensive treatment in an Emergency Department or at the site for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

SAEs that are related to the investigational drug and continue beyond the normal collection period (i.e., are ongoing at the time a subject exits the study) will be followed until resolution or until stabilized with sequelae. SAEs that begin after the subject's

participation in the study is complete, but that the Investigator considers to be related to study drug, may be reported at any time.

The Investigator or clinical site personnel must notify Medivation's vendor PPD and the **Medivation's Medical Monitor** of all SAEs, regardless of relationship to the **investigational drugs**, within 24 hours of clinical site personnel becoming aware of the event.

The Investigator will provide the initial notification by sending a completed Medivation-provided, study-specific "Serious Adverse Event Report" Form", which must include the Investigator's assessment of the relationship of the event to investigational drug, and must be signed by the Investigator.

In addition, notification is sent by the Investigator to the IEC, and the subject's General Practitioner, if applicable.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly as per all SAEs to Medivation's vendor PPD and Medivation Medical Monitor.

All SAE (initial and follow-up) reports should be sent to the SAE reporting contacts provided on [Page 4](#).

8.2.4 Suspected Unexpected Serious Adverse Reactions

A SAE the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product) and which has reasonable relationship to IMP administration is called a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The Sponsor (Medivation Drug Safety) will determine which talazoparib SAEs meet regulatory reporting requirements as a SUSAR. Medivation Drug Safety will:

1. Submit all SUSARs to the local competent authority and global authorities, as required applicable regulatory authorities
2. Issue SUSAR to CCI and/or Investigator whose responsibility will be to report the SUSAR to the applicable IECs

Talazoparib SUSARs will derive from this study as well as other talazoparib clinical studies and will require regulatory reporting as applicable (subjects treated with talazoparib only) for cross-reporting to the local competent authority.

8.2.5 Follow-up of Adverse Events

Follow-up of AEs will continue until resolution, stabilization or death. In case of ongoing AEs at the moment of database closure, the data obtained at the moment of database closure will be used in the statistical analysis. The follow-up of the AE will be documented in the source documents and will be described in the final report only if considered relevant by the Investigator.

8.3 Pregnancy

Pregnancies occurring up to 90 days after the completion of the study drug must be reported to the Investigator. The subject should be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known.

The Investigator should report all pregnancies of female clinical study subjects to Medivation's vendor PPD [REDACTED] and Medivation's Medical Monitor within 24 hours of becoming aware of them using the Pregnancy Reporting Form via email PPD [REDACTED] (United Kingdom) or designated regional toll-free numbers as per the contact information provided on [Page 4: SAE Contact Information](#).

If the Investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, the pregnancy should be reported to Medivation's vendor PPD [REDACTED] and Medivation's Medical Monitor within 24 hours of obtaining written consent from the pregnant partner.

CCI [REDACTED] must report all pregnancies (subject or subject partner) to the Sponsor. Pregnancy outcome will also be reported to the Sponsor within 24 hours of awareness. The Investigator will make arrangements for the partner to be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the partner should continue until the outcome of the pregnancy is known.